Review Article

Management of Hypertension in Patients with COVID-19: Implication of Angiotensin-Converting Enzyme 2

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Abstract

The global coronavirus disease-19 (COVID-19) pandemic, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has created an unprecedented, global public health crisis. Epidemiological studies showed that hypertension is a frequent comorbidity, as well as an independent prognostic risk factor in patients with COVID-19. Angiotensin-converting enzyme-2 (ACE-2) is a receptor for SARS-CoV-2, and thus essential for viral entry into human cells. This review summarizes the recent findings of epidemiology of hypertension in COVID-19 patients and highlights the critical role of ACE2. We also review the impact of endothelial dysfunction, inflammation, and arterial stiffness in promoting hypertension and cardiovascular disease in COVID-19 patients. This review also discusses therapeutic strategies for managing hypertension in patients with COVID-19, with particular emphasis on ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers.

Keywords: *Angiotensin converting enzyme; COVID-19; Hypertension*

Introduction

Data published in August 2021 from the Johns Hopkins Coronavirus Resource Center (coronavirus.jhu.edu) suggest that more than 200 million coronavirus disease-19 (COVID-19) cases have been reported worldwide, profoundly changing our lives.[1] COVID-19 is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and initially targets the lungs.[2,3] Studies suggest that there often is a subsequent complex and detrimental interaction between COVID-19 and cardiovascular diseases (CVDs). Typically, COVID-19 patients with underlying comorbidities often present with CVD, such as hypertension, myocarditis, heart failure, arrhythmias, and thromboembolic disease in both the acute and long-term settings.[4] Hypertension is one of the most prevalent CVD in COVID-19 patients. Data also indicate that hypertension considerably increases the risk of hospitalization and death.[5] In an early study of 1590 COVID-19 patients in China from December 11, 2019, to January 31, 2020, the most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%).[6] Recent data suggest that untreated or uncontrolled hypertension increases the risk of infected patients becoming severely ill.[7,8] Of note, patients with untreated or uncontrolled high blood pressure seem to be at a higher risk of developing complications from COVID-19 than those whose high blood pressure is well controlled with medical treatment.[7,8] The mortality rate in COVID-19 patients with hypertension has been reported to be 7.9% (11/140) in patients who were not taking antihypertensive drugs versus 3.2% (23/710) in those who were taking antihypertensive medications, with 2.17-fold increased risk after adjusting for confounding factors.[9] The correlation between COVID-19 and hypertension has been linked to angiotensin converting enzyme 2 (ACE2), a member of the renin-angiotensin-aldosterone system (RAAS) and as well as a receptor through which SARS-CoV-2 enters cells. This review highlights recent studies evaluating the role of ACE2, gives a brief overview of RAAS

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regulation and COVID-19 associated hypertension, provides a contemporary understanding of the roles of ACE2 in hypertensive patients with COVID-19, and discusses therapeutic strategies.

Epidemiology of Hypertension in COVID-19 Patients

Hypertension is an important risk factor for other CVDs, including coronary artery disease, stroke, and heart failure.[10-12] In the 2020 International Society of Hypertension Global Hypertension Practice Guidelines, hypertension is defined as systolic blood pressure at ≥140 mm Hg and/or diastolic blood pressure at ≥90 mm Hg on repeated examination.[13] Many risk factors, including older age, the Black race, family history, obesity, smoking and high sodium intake, are implicated in the pathogenesis and progression of hypertension.[10] Recent studies found much higher incidence of CVD in COVID-19 patients with hypertension. During the initial pandemic period in China, 20%–51% of COVID patients presented with at least one complication, including diabetes (10%–20%), hypertension (10%–15%) as well as CVDs and cerebrovascular diseases (7%–40%).[14] In a study of 41 patients in China, 15% of the COVID-19 patients (median age: 49 years; 73% men) had hypertension.[15] A case-series study of 5,700 patients with SARS-CoV-2 infections in the New York metropolitan area showed that the most common comorbidities were hypertension (3026; 56.6%), obesity (1737; 41.7%), and diabetes (1808; 33.8%).[16] In a retrospective study of 776 adults with COVID-19 infection in New Orleans, 73.8% of the hospitalized patients had hypertension.[17] Overall, hypertension, obesity, and diabetes, and the Black race are the most important risk factors for hospitalization.[17] Therefore, hypertension is the one of the most prevalent comorbidities among COVID-19 individuals and is a key predictor for complications requiring hospitalization.

Hypertension is an independent and powerful prognostic risk factor in patients with COVID-19. In a study of 72,314 individuals with COVID-19, case fatality rate was 2.3% in the overall study population, but much higher in patients with hypertension (6.0%), diabetes (7.3%), and CVDs (10.5%).[18] In a retrospective cohort study of 3988 COVID-19 patients, hypertension was the most common comorbidity and its presence significantly increased mortality risk.[19] The OpenSAFELY analysis of 17,278,392 patients in England found that hypertension was related to a markedly increased risk of death in COVID-19 patients.[20] Moreover, older age was strongly related to hypertension as evidenced by a higher hypertension risk for individuals up to 70 years of age.[20] Furthermore, all nonwhite ethnic groups had higher risk than white ethnicity. Compared to individuals of white ethnicity, black (hazard ratio 1.48) and South Asian (hazard ratio 1.45) people have increased risk of hypertension.[20] Similar findings were reported in another study in young US adults hospitalized with COVID-19, which showed that 57% were Black or Hispanic and 16.1% of those had hypertension. Moreover, hypertension, obesity, and the male sex correlate with a higher risk of death or mechanical ventilation.[21] Disparities in healthcare access and socioeconomic status between ethnic groups may affect COVID-19 morbidity. Individuals with lower socioeconomic status had higher risk of contracting COVID-19.[22] These data indicate that hypertensive patients have a greater mortality risk when compared with nonhypertensive individuals with COVID-19.

Individuals with metabolic disorders, including insulin resistance, diabetes, and cardiometabolic syndrome, have a high prevalence of hypertension.[11] Indeed, both hypertension and diabetes are common clinical complications in patients with COVID-19.[14,16] Recent data from 18,012 COVID-19 patients found that the occurrence of diabetes and hypertension were moderately associated with severity and mortality for COVID-19.[23] Another study of 15,794 COVID-19 patients found that hypertension and diabetes were related to admission to intensive care unit and mortality.[24] However, one recent study from England failed to show an association between hypertension and mortality in COVID-19 patients with type 1 diabetes.[25] Interestingly, hypertension was weakly related to lower COVID-19-related mortality in patients with type 2 diabetes.[25] Further investigations are needed to understand the precise interaction of hypertension and diabetes in COVID-19 patients.

RAAS and Hypertension: Implications for Patients with COVID-19

The RAAS plays an important role in regulating blood pressure. In response to intravascular volume contraction and low blood pressure, sympathetic nervous activity is increased to promote renin secretion by renal juxtaglomerular cells, which in turn catalyzes the formation of angiotensin I (Ang I) from angiotensinogen, which is released from the liver.[26] Ang I is then cleaved by ACE, producing Ang II, which binds the Ang II type 1 receptor (AT1R) and results in vasoconstriction, inflammation, oxidative stress, fibrosis, apoptosis, and cellular proliferation, as well as increased adrenal aldosterone secretion and secretion of antidiuretic hormones, all of which lead to an increase of blood pressure [Figure 1].[10,26] In contrast, ACE2, a membrane-bound monocarboxypeptidase expressed in cardiovascular

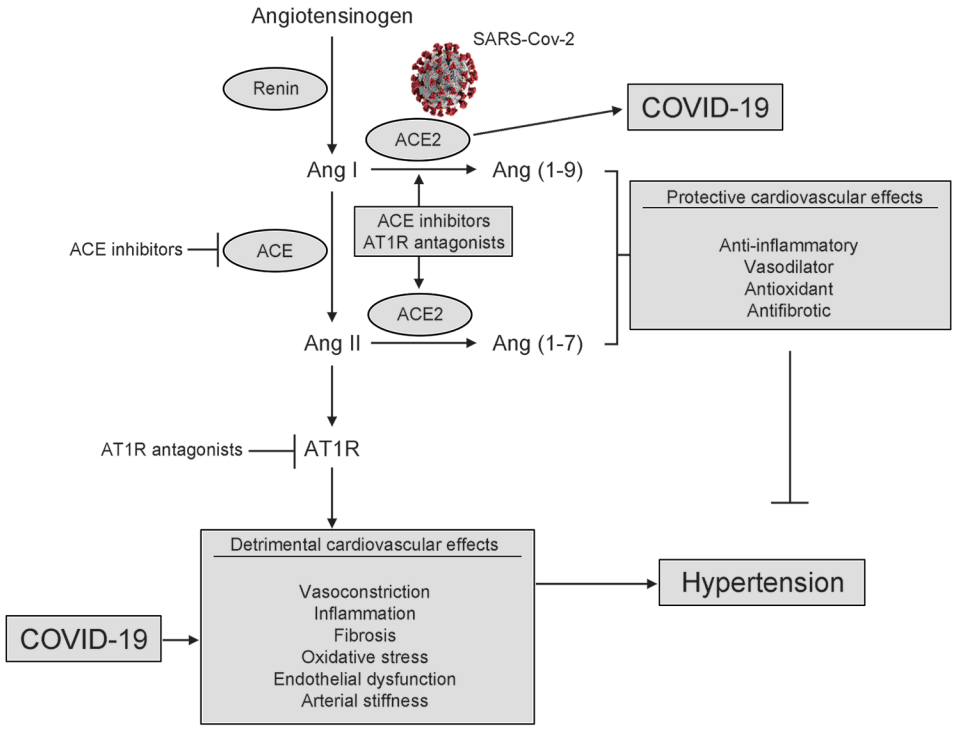

Figure 1: Proposed mechanism of ACE2 in a connecting link between blood pressure regulation and SARS-CoV-2 infection.

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-19, ACE: Angiotensin converting enzyme, Ang: Angiotensin, AT1R: Ang II type 1 receptor

tissues, the kidneys, lungs, and liver tissues, converts Ang II to Ang (1-7) and Ang I to Ang (1-9).[26] Ang (1-7) mediates many beneficial effects, such as vasodilation through the release of nitric oxide and prostaglandins through the MAS receptor [Figure 1].[26] Abnormally active RAAS is the target of many antihypertensive drugs. For instance, ACE inhibitors decrease Ang II production. AT1R antagonists inhibit the overactive RAAS by inhibiting the binding of Ang II to AT1R [Figure 1].[26] Basic and clinical studies indicate that increased ACE2 expression reduces blood pressure whereas reduced ACE2 contributes to increased blood pressure.[26]

Angiotensin Converting Enzyme 2 as a Link between Blood Pressure Regulation and Severe Acute Respiratory Syndrome-Coronavirus-2 Infection

ACE2 is of particular interest in COVID-19 because this component of the RAAS is critically involved in both SARS-CoV-2 entrance into the respiratory tract as well as the pathophysiology of hypertension. Specifically, ACE2 is a high-affinity receptor for the SARS-CoV-2 spike protein and facilitates viral attachment to the respiratory epithelial cell surface [Figure 1]. ACE2 expression is also found in human vascular endothelial cells, cardiomyocytes, renal tubules, gallbladder, male reproductive cells, and eye tissues, with low expression in the respiratory tract under normal conditions.[27] Recent data showed that the expression of ACE2 is repressed with the onset of COVID-19 infections.[28-30] Reduced ACE2 promotes the detrimental role of ACE-Ang II-AT1R signaling loop and decreases the protective role of ACE2-Ang-(1-7) axis. Further, the downregulation of ACE2 activates the bradykinin 1 and 2 receptors to induce angioedema and vascular leakage, facilitating lung injuries in COVID-19 patients.[31,32] Thus, decreased ACE2 expression increases the levels of Ang-II in local tissue, leading to lung injuries and blood pressure elevation. Indeed, increased circulating Ang-II has been found in COVID-19 patients, and correlated with increased viral load and lung injury.[28,33] Thus, reduced ACE2 in SARS-CoV-2 infection induces the dysregulation of the RAAS and related increased Ang II levels in the vasculature, leading to a proinflammatory and procoagulant state in patients with COVID-19.

COVID-19 promotes the expression of disintegrin and metalloproteinase 17, which promote ACE2 shedding in host cells, resulting in compromised ACE2 function while increasing Ang II and ACE expression. Increased Ang II also exacerbates the release of inflammatory

cytokines. Increased plasma ACE2 has also been found in COVID patients with mild or moderate symptoms/complications.[31,34] This may explain the persistent symptoms after the initial COVID-19 infection. The expression of ACE2 is distinct in different parts of the respiratory system. RNA mapping showed that highest ACE2 expression in the nose, with decreasing expression down the respiratory tract; such a pattern is paralleled by the decreasing gradient of SARS-CoV-2 infection from proximal to distal respiratory tract.[35] High-risk tissues include the lower respiratory tract (2%), ileum (30%), heart (>7.5%), kidney (4%), bladder (2.4%), lung (>1%), and esophagus (>1%).[36] The liver and stomach tissues had <1% proportion of ACE2-positive cells and are regarded as having low risk for conveyance of SARS-CoV-2 infection.[36]

In a recent study that analyzed 30 tissues in thousands of COVID-19 patients, tissue ACE-2 levels were significantly higher in Asian women compared to men and other racial groups.[37] There was an age-dependent reduction in ACE-2 levels and a marked reduction in diabetic patients.[37] The gene that encodes ACE2 is located in the X chromosome; as such, men have only one alleles and thus tend to have lower ACE-2 expression.[37] However, one prospective single-center study showed that serum ACE2, Ang II, and aldosterone levels were unaltered in COVID-19 patients.[38] Further studies are needed to elucidate the role of ACE2 in the interplay between hypertension, CVD, and COVID-19 severity.

Endothelial Dysfunction and Arterial Stiffening Promote Hypertension in COVID-19 Patients

Endothelial dysfunction is a key element in the pathogenesis of COVID-19-related hypertension.[26] In response to various biochemical and physical stimuli, arterial endothelial cells release a variety of vasoactive substances, including both vasodilators (e.g., nitric oxide, endothelium-derived hyperpolarizing factor, prostacyclin) and vasoconstrictors such as Ang II.[26] Enhanced RAAS activity increases oxidative stress and inflammation by reducing nitric oxide production, thereby leading to impaired endothelial-mediated arterial relaxation.[26] Further, SARS-CoV-2 infection can lead to direct endothelial damage through increased subintimal inflammation, hemorrhage, and thrombosis. Increased matrix metalloproteinase production also promotes adverse functional and structural arterial remodeling.[39] Endothelial dysfunction and associated hypercoagulability are also involved in the development of COVID-19 related morbidity and mortality. For instance, studies found that 72% of deaths had evidence of hypercoagulability,[40] and serum VWF levels were significantly increased in patients with COVID-19.[41]

Previous work from this laboratory showed that inappropriate RAAS activation and endothelial dysfunction could induce arterial stiffening and subsequent hypertension.[10,42] Excessive arterial stiffness typically precedes hypertension, and the arterial functional and structural abnormalities underlying excessive arterial stiffness often exist prior to hypertension.[10,42] The interplay of SARS-CoV-2 and inappropriate RAAS activation may play an important role in the development of arterial stiffening and subsequent hypertension. In a case-control study of 22 COVID-19 patients versus 22 sex-and age-matched individuals, COVID-19 was independently associated with higher pulse wave velocity (PWV), a measure of increased arterial stiffness.[43] The study also showed that increased PWV contributed to longer hospital stay and higher mortality.[43] A cross-sectional study showed that, in comparison to young healthy volunteers, young COVID-19 patients had markedly impaired vascular function as defined by impaired flow-mediated dilation of the brachial artery and increased arterial stiffness as determined with carotid-femoral PWV.[44] A multicenter, retrospective cohort study of 12,170 individuals with COVID-19 showed that arterial stiffness, defined as pulse pressure ≥60 mm Hg, was related to greater risk of all-cause mortality in hospitalized COVID-19 patients.[45] This correlation was independent of other comorbidities, including gender, age, and the presence of hypertension or antihypertensive treatment.[45]

Inflammation Contributes to Development Hypertension in COVID-19 Patients

Inappropriate activation of the RAAS increases systemic and vascular inflammation and contributes to the development of vascular injury and hypertension. Both Ang II and aldosterone increase the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and IL-8.[10,42] Studies showed that activated nuclear factor kappa B (NF-κB) and toll-like receptor 4 (TLR4) are involved in vascular injury and hypertension associated with increased RAAS activation. For instance, Ang II infusion increased TLR4 signaling and activated NF-κB signaling and inflammatory responses, resulting in arterial dysfunction.[46] Ang II also increases the release of inflammatory cytokines via TLR4 signaling.[47] Further, RAG-1$^{-/-}$ mice that lack T-and B-lymphocytes have reduced arterial stiffness and lower blood pressure versus the wild type control.[48,49] In contrast, deficiency of T-regulatory cells increased Ang II-induced arterial

oxidative stress, inflammatory responses, arterial stiffness, and hypertension.[48,49] These data suggest that activated RAAS and associated immune mediated inflammation may play an important role in the pathogenesis of hypertension in patients with COVID-19.

Acute cytokine storm and chronic inflammatory responses are major pathophysiological processes of COVID-19. The cytokine storm is characterized by increased erythrocyte sedimentation rate, C-reactive protein, TNF-α, IL-1β, IL-6, IL-8, granulocyte-colony stimulating factor, interferon gamma-induced protein-10, and macrophage inflammatory protein-1 alpha.[50,51] These inflammatory cytokines recruit immune cells from the systemic circulation to the site of tissue infection, leading to impaired endothelial cell-cell interactions, capillary damage, diffuse alveolar injury, and multiple organ failure.[50,51] Inflammatory cytokines also activate platelets and leukocytes to form neutrophil extracellular traps, resulting in a pro-thrombotic state and formation of microvascular thrombi.[52] Hypoxia elevates fibrinogen degradation products, which in turn promote disseminated intravascular coagulation.[52] Moreover, SARS-CoV-2 infection impairs mitochondrial dysfunction and increases mitochondrial reactive oxygen species production, and by doing so, contributes to the inflammatory response and vascular injury.[53] One study in the UK Biobank population showed that there was a positive correlation between increased monocyte, lymphocyte, and neutrophil counts, and hypertension.[54] Another clinical study also found that both CD4+ and CD8+ lymphocytes were dysregulated in hypertension, with increased production of proinflammatory cytokines, including IL-6, interferon gamma, and TNF-α.[55] Furthermore, chronic inflammatory responses are related to vascular injury endothelial dysfunction, vascular stiffening and hypertension in COVID-19 patients.

Therapeutic Strategies in Hypertensive Patients with COVID-19

COVID-19 drugs

Remdesivir (Veklury), is an inhibitor of RNA polymerase originally used to treat Ebola infections and is now used to treat COVID-19 patients. Preclinical studies suggest that remdesivir and chloroquine might potentially block virus infection at micromolar concentrations.[56] Ongoing clinical trials are investigating the efficacy of remdesivir treatment alone or in combination with chloroquine in COVID-19 patients.[56] The FDA has approved the emergency use of baricitinib (Olumiant), an anti-rheumatoid arthritis medication with anti-inflammatory and antiviral activity, to treat COVID-19 patients.[57] Baricitinib can be used in patients who are hospitalized with COVID-19 not requiring supplemental oxygen or mechanical ventilator support.[57]

ACE2 soluble proteins prevent the entry of SARS-CoV-2 into cell lines by saturating the virus binding sites,[58] and have been explored as a potential treatment of acute respiratory distress syndrome associated with COVID-19 infections. This possibility remains to be evaluated in animal and human studies.

COVID-19 patients have increased risk of venous thromboembolism. In a meta-analysis of 66 studies from 28173 patients, the overall prevalence of venous thromboembolism was 14.1% in patients with COVID-19, and 22.7% among those admitted to intensive care units.[59] However, available evidence does not support prophylactic use of therapeutic-dose heparin and low-molecular-weight heparin in thrombosis prevention in patients with severe COVID-19.[60] Whether intermediate or therapeutic doses of thromboprophylactic drugs are safe and effective in moderately ill patients with COVID-19 also needs further elucidation.[60]

Dexamethasone decreases the risk for death by about 30% in COVID-19 patients on ventilators and by about 20% in patients who needed supplemental oxygen. Dexamethasone is the only effective therapy in hospitalized COVID-19 patients in the RECOVERY trial.[61] Drug repurposing of different available antiviral drugs, such as immune-based therapy, hydroxychloroquine, and chloroquine, has been used to identify potential combination treatments.

Antihypertensive drugs

Inhibiting ACE2 could hamper the entry of SARS-COV2 into host cells, and thus represent a treatment strategy for COVID-19, but may not be compatible in patients with hypertension since ACE2 inhibition could increase Ang II and AT1R activity, leading to inflammation and oxidative stress, and associated hypertension and CVD.

The most commonly used drugs in hypertension treatment are ACE inhibitors, AT1R antagonists, calcium channel blockers (CCBs), and beta-blockers.[10] Both ACE inhibitors and AT1R blockers exert their effects through decreasing the detrimental effects of RAAS activation. ACE inhibitors and AT1R antagonists can increase ACE2 activity [Figure 1], and thus may increase the risk of SARS-COV2 infection and aggravate disease in COVID-19 patients. A meta-analysis of 2,100,587 participants showed that anti-hypertensive drugs, including ACE inhibitors, AT1R antagonists, beta-blockers, thiazide diuretics, and CCBs were not associated with increased risk for infection or disease severity of COVID-19.[62] The Randomized Elimination

and Prolongation of ACE inhibitors and AT1R blockades in Coronavirus 2019 (REPLACE COVID trial) investigated the outcome of continuation versus discontinuation of RAAS inhibitors in hospitalized patients with COVID-19. Results showed no difference in the severity of COVID-19 infection between the two groups.[63] A recent cohort study enrolling two million hypertensive patients showed that both ACE inhibitors and AT1R antagonists were related to lower risk of COVID-19 hospitalization versus CCBs. Patients with COVID-19 taking ACE inhibitors or AT1R antagonists also had lower risk of intubation and death versus CCBs.[64] In contrast, withdrawal of ACE inhibitors and AT1R antagonists was related to higher mortality in hospitalized individuals with COVID-19.[65] Based on these findings, the European Society of Cardiology and the International Society of Hypertension recommended continuation of using ACE inhibitors and AT1R antagonists in patients with COVID-19.[66] CCBs also improved prognosis of hypertensive patients with COVID-19. In a retrospective cohort study from 1078 COVID-19 patients, individuals using CCBs had lower mortality (1.95% vs. 5.85%) than non-CCBs group.[67] A meta-analysis of 119,298 COVID-19 patients from 31 studies showed that CCBs usage was not associated with the outcome of COVID-19 but was associated with a decreased mortality rate.[68] Indeed, CCBs have also been found to be protective against influenza A virus, dengue fever, and Zika virus infection.[69-71] Beta-blockers decrease ACE2 receptors expression and cluster of differentiation 147,[72] and thus might be antihypertensive agents in COVID-19 patients with comorbidities such as heart failure and atrial fibrillation. However, the current evidence of the potential mechanism of beta-blockers in COVID-19 remains scarce.

Summary and Future Perspectives

COVID-19 increases the prevalence of hypertension and CVD. ACE2 is a link between blood pressure regulation and SARS-CoV-2 infection. Endothelial dysfunction, excessive arterial stiffness, and inflammation all promote COVID-19 related hypertension and CVD. Treatment modalities in hypertensive patients with COVID-19 include antivirus and antihypertensive therapies. ACE inhibitors, AT1R antagonists, and CCBs are appropriate in the treatment of hypertension in COVID-19 patients. However, most data analyzing different antihypertensive classes are from retrospective investigations or meta-analyses. Multiple-center randomized trials are needed to better define the therapeutic role of these antihypertensive medications in patients with COVID-19. Further, more clinical studies evaluating the association between RAAS activation, hypertension, and COVID-19 infection may lead to more targeted therapeutic strategies in the future.

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Conflicts of interest

There are no conflicts of interest.

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